

Appln. No. 10/666,335
Amd. dated February 19, 2008
Reply to Office Action of September 19, 2007

REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 20-24 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 20-24 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, which being enabling for a pharmaceutical composition comprising a TNF antagonist, does not reasonably provide enablement for a pharmaceutical composition comprising a TNF antagonist and either hCG, LH or FSH. The examiner holds that the specification demonstrates that administering TNF antagonists ameliorates endometriosis and a pharmaceutical composition comprising a TNF antagonist is enabled. However, the examiner takes the position that patients suffering from endometriosis should be treated with antagonists of gonadotropin hormones, not with the hormones themselves, citing Sharpe et al., Ling, and Funk et al. Furthermore, the examiner states that, even if the pharmaceutical composition were enabled for treating endometriosis, it would not be enabling for treating infertility because while endometriosis might result in infertility, not all

infertility is caused by endometriosis. This rejection is respectfully traversed.

Claim 20 is now amended to recite "treating endometriosis-related infertility", as supported at page 7, lines 1-4, of the present specification. Accordingly, the claims are now directed only to endometriosis-related infertility and do not encompass all causes of infertility.

With due respect to the examiner, the examiner's understanding of the prior art teachings is incorrect. It may be true that endometriosis under certain circumstances is treated with antagonists of gonadotropin hormones or with gonadotropin-releasing hormone (GnRH) agonists which lead to a desensitizing of the GnRH receptor and are therefore functionally equivalent to antagonists of gonadotropins (Huirne JA, Lambalk CB, Gonadotropin-releasing-hormone-receptor antagonist, *Lancet*. 2001 Nov 24; 358(9295):793-8031, a copy of which is attached hereto. This treatment may be applied when the main symptom of endometriosis to be treated is pelvic pain.

The situation is, however, completely different when the main symptom of the endometriosis to be treated is infertility or subfertility, and an improved fecundity rate is

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to be achieved. In this situation, treatment with GnRH agonists had not been shown to be effective in the treatment of endometriosis-related infertility and was therefore not recommended. See Adushi et al., Editors, *Reproductive Endocrinology, Surgery, and Technology*, 1996, Lippincott-Raven Publishers, Vol. 2, p. 2131, a copy of which is attached hereto, which teaches in the right column of page 2131.

In summary, GnRHa has not been shown to enhance fertility in patients with endometriosis.

In view of the functional equivalence of GnRH agonists with antagonists of gonadotropins, the skilled artisan would also not have expected antagonists of gonadotropins to be useful for treatment of endometriosis-related infertility.

To the contrary, endometriosis-related infertility is and was indeed treated in the art with gonadotropins, frequently in combination with surgery and/or assisted reproduction techniques (see p. 375, left column, 3rd paragraph ff. of De Hondt A, Meuleman C, Tomassetti C, Peeraer K, D'Hooghe TM, Endometriosis and assisted reproduction: the role for reproductive surgery? *Curr Opin Obstet Gynecol*. 2006 Aug; 18(4):374-91, a copy of which is attached hereto). This was already in practice by the skilled artisan at the effective

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filing date of the present application (see Kemmann E, Ghazi D, Corsan G, Bohrer MK, Does ovulation stimulation improve fertility in women with minimal/mild endometriosis after laser laparoscopy?, *Int J Fertil Menopausal Stud.* 1993 Jan-Feb; 38(1):16-211), a copy of which is attached hereto.

Also attached hereto is a copy of Goker et al. Controlled ovarian hyperstimulation and intrauterine insemination for infertility associated with endometriosis: a retrospective analysis. *Arch. Gynecol. Obstet.* 266-21-24 (2002), that further supports the use of gonadotropin hormones in treating endometriosis-related infertility. Accordingly, the presently claimed pharmaceutical composition, comprising an anti-TNF antibody or a fragment thereof in combination with a gonadotropin hormone, is indeed enabled for treating endometriosis-related infertility.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the present claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their

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allowance. Favorable consideration and early allowance are
earnestly urged.

Respectfully submitted,

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